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| EXAMINER | |
|---|---|
| RIGGS II, LARRY D | |

| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/612,356 | ZAHN ET AL. | |
| | Examiner | Art Unit | |
| | Larry D. Riggs II | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendments and request for reconsideration filed 18 September 2007 are acknowledged and entered.

### *Drawings*

Deletion of figure 8 is acknowledged.

### *Status of Claims*

Claims 1-29 are currently pending. Claims 1-9 are under consideration on the merits.

### *Claim Objections*

Claims 4-6 are objected to because of the following informalities:

Claim 4 provides "solubule" in line 4. It is suggested that applicant recite the limitation as "soluble" to result in grammatical correctness.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112, 2nd Paragraph*

The rejection of claims 1 and 7-9 under 35 U.S.C. 112, 2nd Paragraph in the Office action mailed 18 June 2007 is withdrawn in view of the arguments filed 18 September 2007.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

**The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claim 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "recombinant amyloidogenic proteins to form a mixture" in lines 4-5. The metes and bounds are unclear as whether the recombinant amyloidogenic proteins refer to multiple molecules of the same protein or actually different recombinant proteins, i.e. proteins with different sequences and/or structures?

Claim 3 recites the limitation "significantly below critical micelle concentration" in lines 8-9. The metes and bounds of the limitation are unclear as what would suffice as being significantly below the critical micelle concentration.

Claim 3 recites the limitation "and treatment of the so produced amyloidogenic aggregates with non-denaturing detergents" in lines 9-10. The metes and bounds of the limitation are unclear. One skilled in the art would not know if the aggregates in step b) are produced as a result of dilution of the solution of water soluble complexes or as a result of dilution and addition of non-denaturing detergents. The preamble implies that the result of each step in claim 3 may result in the production of amyloidogenic aggregates and it is unclear when the resulting aggregates are produced in step b) of the instant claim.

Claim 4 recites the limitation "amyloidogenic oligomeric B-sheet intermediate structure is an oligomeric B-sheet intermediate ($PrP^{\beta}$)" in lines 4-5. The metes and

bounds are unclear. One skilled in the art would not understand how a B-sheet structure is an intermediate protein.

Claim 9 recites the limitation "the pH of the conversion buffer is below the isoelectric point of the recombinant amyloidogenic proteins" in lines 1-3. The metes and bounds are unclear. If there are plural types of amyloidogenic proteins in the solution, each assumingly having their own isoelectric point, one skilled in the art would not know what pH would suffice to be below "the isoelectric point" as recited in line 2 of the instant claim.

***Claim Rejections - 35 USC § 102***

The rejection of claims 1 and 9 under 35 U.S.C. 102(b) over Martinez-Senac et al. and Esler et al., in the Office action mailed 18 June 2007 is withdrawn in view of the arguments filed 18 September 2007.

***Claim Rejections - 35 USC § 103***

The rejection of claims 1-9 under 35 U.S.C. 103(a) over Martinez-Senac et al. in view of Barrow et al. in view of Bursky et al. in view of Luhrs et al. in view of Pan et al. and in view of Vold et al. in the Office action mailed 18 June 2007 is withdrawn in view of the arguments filed 18 September 2007.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al.

The instant claims are drawn to a method for increasing the content of B-sheet secondary structure in recombinant amyloidogenic proteins by mixing negatively charged lipids with amyloidogenic proteins at a temperature and exposing the mixture to

a conversion temperature for a time sufficient to increase the B-sheet secondary structure in the proteins.

Kleinschmidt et al. shows a method for increased B-sheet formation when Outer Membrane Protein A folds into a Beta Barrel as it inserts into a lipid bilayer, (DOPC is negatively charged at pH 8.5, see figure 1), at various temperatures, (see page 5011, right column, second paragraph, Figure 6).

Kleinschmidt et al. does not show the method utilizing an amyloidogenic protein.

Pan et al. shows the conversion of alpha-helices into beta-sheets of amyloid proteins.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of observing increased beta-sheet formation with the insertion of protein into a lipid bilayer of Kleinschmidt with use of amyloid proteins by Pan et al. because by Pan shows attempts of producing beta-sheet containing soluble amyloid protein, (see page 10965, second paragraph - page 10966, last paragraph).

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al. and Barrow et al.

Kleinschmidt et al. is applied as above to claim 1.

Regarding claims 2 and 3, Martinez-Senac et al. teaches the increased beta-sheet formation of amyloid peptide when interacting with negatively charged phospholipids vesicles, (see page 746, left column, fifth paragraph; page 751, left

column, second paragraph). Martinez-Senac et al. teaches the preparation of amyloid peptide in association with negative charged phospholipids dissolved in water formed fibrils, (see page 747, left column, second paragraph).

Kleinschmidt et al. in view of Pan et al. in further view of Martinez-Senac et al. do not teach actively destroying the lamellar lipid structures.

Barrow et al. teaches that once a beta-sheet structure is formed in amyloids, the structure leads to the formation of insoluble amyloid fibrils, (page 253, middle column, first paragraph – right column, second paragraph). Barrow et al. teaches that in aqueous solutions, in the absence of TFE, at either low or high pH the amyloid peptides are 100% beta-sheet, causing an insoluble gel to form (page 253, middle column, first paragraph – right column, second paragraph).

One would be motivated to disperse the micelles surrounding amyloid protein with the advantage of showing the amyloid protein was increasing in beta-sheet secondary structure with the formation of insoluble fibrils that occur when amyloid protein is exposed to water. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Martinez-Senac et al. by putting the vesicles in an environment, such as pure water, that would destroy the micelles surrounding the amyloids to produce the insoluble amyloid fibrils as implied by Martinez-Senac et al. and taught by Barrow et al.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al. and Gursky et al.

Kleinschmidt et al. is applied as above to claim 1.

Regarding claims 4 and 5, Marinez-Senac et al. teaches the increase of beta-sheet formation in amyloids with negatively charged vesicles, (see above).

Kleinschmidt et al. in view of Pan et al. in further view of Marinez-Senac et al. do not teach the increase in beta-sheet formation with increase in temperature.

Gursky et al. provides a method for the temperature-dependent beta-sheet formation in amyloids in water. Gursky et al. teaches the increase of beta-sheet formation with the increase of temperature from 0 to 98°C at a rate of 15 deg/h, (see figure 2, page 98, right column, last paragraph – page 99, right column, first paragraph).

One would be motivated to increase the temperature of the solution of amyloid and vesicles with the benefit of increasing the interaction of the phospholipids and the amyloid peptide and thus increase in beta-sheet formation. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Marinez-Senac et al. by increasing the temperature once all components of the mixture were added as taught by Gursky et al.

Claims 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al. and Luhrs et al. (IDS) and Vold et al.

Kleinschmidt et al. is applied as above to claim 1.

Regarding claim 6, Marinez-Senac et al. teaches the increase of beta-sheet formation in Alzheimer beta-amyloid peptide, with negatively charged vesicles.

Kleinschmidt et al. in further view of Marinez-Senac et al. do not teach utilizing amyloidogenic proteins involved in Transmissible Spongiform Encephalopathy (TSE).

Luhrs et al. teaches the use of amyloid protein involved in Transmissible Spongiform Encephalopathy (TSE), (see introduction) in monitoring beta-sheet formation in negatively charged vesicles, (see figure 1, 3 and conclusion). Pan et al. teaches the conversion of alpha-helices into beta-sheets in the formation of the scrapie prion proteins. Pan et al. teaches that the conversion of alpha-helices in the prion protein into beta-sheets is likely to be the primary lesion in the illness of Spongiform Encephalopathy, page 10965, second paragraph). Pan et al. teaches similar proteins that undergo the conversion of alpha-helices into beta-sheets are betaA4 peptides involved in Alzheimer disease, (see page 10966, first paragraph).

One would be motivated to utilize other proteins that undergo beta-sheet formation that have the propensity to form insoluble fibrils with the benefit of showing the method was applicable to other amyloid class proteins and their associated diseases. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Marinez-Senac et al. by utilizing a protein associated with Transmissible Spongiform Encephalopathy (TSE).

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al. and Vold et al.

Kleinschmidt et al. is applied as above to claim 1.

Regarding claims 7 and 8, Martinez-Senac et al. teaches the increased beta-sheet formation of amyloid peptide when interacting with negatively charged phospholipid vesicles, made from DMPC, DMPS, DMPG and other members of the phosphocholine family (see page 745, left column, third paragraph).

Kleinschmidt et al. in view of Pan et al. in further view of Martinez-Senac et al. do not teach the preparation of negatively charged vesicles with DMPX or DHPC.

Vold et al. teaches magnetically oriented phospholipid bilayered micelles for structural studies of polypeptides. Vold et al. teaches the binary mixture of long and short chain phosphatidylcholines such as DMPC and DHPC to be consistent with disk-shaped phospholipid aggregates, (see page 267, left column, first paragraph).

One would be motivated to utilize other phosphocholine family members that allowed for the production of charged phospholipid bilayered micelles for the benefit of exploiting lipids that may be more appropriate for particular biological systems. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Marinez-Senac et al. by utilizing other phosphocholine family members such as DMPX or DHPC.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al.

Kleinschmidt et al. is applied as above to claim 1.

Kleinschmidt et al. in view of Pan et al. do not teach a conversion buffer with the pH below the isoelectric point of the recombinant amyloidogenic proteins.

Regarding claim 9, Martinez-Senac et al. teaches buffer pH at 3.0, (see figures 3 and 4). This pH is below the beta amyloid peptide isoelectric point of 5.0, (see page 13919, second column, second paragraph).

One would be motivated to use buffers with pH below the isoelectric point of amyloid proteins with the benefit of increase in beta-sheet formation without aggregation. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Kleinschmidt et al. in view of Pan et al. by using low pH conversion buffer as taught by Martinez-Senac et al.

## ***Conclusion***

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry D. Riggs II whose telephone number is 571-270-3062. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LDR/
Larry D. Riggs II
Examiner, Art Unit 1631

/ Shubo (Joe) Zhou/
Shubo (Joe) Zhou, Ph.D.
Primary Examiner